The Peptides

Analysis, Synthesis, Biology

VOLUME 2 Special Methods in Peptide Synthesis, Part A

Edited by

ERHARD GROSS

National Institutes of Health
Bethesda, Maryland

JOHANNES MEIENHOFER

Chemical Research Department
Hoffmann-La Roche Inc.
Nutley, New Jersey

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Chapter 1

Solid-Phase Peptide Synthesis

GEORGE BARANY and R.B. MERRIFIELD

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I. INTRODUCTION

The science and art of peptide synthesis was founded at the beginning of the twentieth century by Emil Fischer and Theodor Curtius, and has steadily been developed into a discipline of great power and sophistication. The classical methodology has been reviewed by Greenstein and Winitz (1961), Schröder and Lübke (1965), Wünsch (1974), Bodanszky *et al.* (1976), Finn and Hofmann (1976), and in these volumes of "The Peptides." However, as recently as 15 years ago, the successful synthesis of biologically active materials still required considerable investments of time, effort, and manpower. Perhaps the most intimidating aspect of the field has been the need to purify, by discriminating methods, all intermediates of lengthy multistep routes, a non-routine and demanding task. The problem is made all the more challenging by the unpredictable solubility characteristics of the various intermediates.

Solid-phase peptide synthesis was conceived in 1959, at a time when chromatography on insoluble resins was being applied with great success to the analysis of amino acids, peptides, and proteins. It was reasoned that by attaching a growing peptide chain to an insoluble polymeric support, excess reagents and by-products from the synthetic cycles could be removed by simple filtration and washing steps. Thus, the purification problem of classical methods of peptide synthesis ought to be readily circumvented, while most of the highly honed chemistry of coupling and functional group protection was expected to be readily adaptable to the new strategy. As an added benefit, the entire solid-phase procedure was predicted to be amenable to automation. The feasibility of these ideas was first shown by the synthesis of the crystalline tetrapeptide L-leucyl-L-alanyl-glycyl-L-valine (Merrifield, 1962, 1963). At about the same time, Letsinger and Kornet (1963) reported the polymer-supported synthesis of L-leucyl-glycine, using a different chemical approach. Further developments followed soon thereafter in several laboratories, and a useful and practical set of methods has evolved that will be the subject of this review.